Structure-activity relationship of plasticins interacting with biomimetic models of bacterial membranes

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Over the past twenty years, the emergence of bacteria resistant to conventional antibiotics has increased the therapeutic needs of original sources. Antimicrobial peptides (AMP) appear to be very interesting candidates for the development of new drug molecules to complement traditional therapies [1]. Plasticins are short, mostly cationic, glycine and leucine-rich linear AMP, extracted from exsudates of amphibians’ skin. We have studied the interactions of two of them with physico-chemical models of bacteria membranes, in order to characterize the molecular mechanisms underlying plasticin adsorption and penetration into those membranes. The natural neutral plasticin PTC-DA1, inactive against the main bacterial strains, was compared to its modified positively charged counterpart, PTC-DA1-KF, which shows a good antibacterial activity [2,3].

Since the structure of bacterial membranes is highly complex with superposition of layers with different compositions, our approach consisted in splitting up the system into models of each layer. We have first studied the interaction of the two peptides with LPS-rich monolayers mimicking the outer leaflet of Gram-negative bacteria membranes. Then, we have analysed their interaction with SOPE/SOPG/cardiolipin (80/15/5) mixed monolayers modelling the inner leaflet of the bacterial membrane. The combination of analytical interfacial techniques such as surface pressure and surface potential measurements, Brewster angle microscopy and quartz crystal microbalance allowed getting a better insight into the self-organization of the peptides at membrane interfaces, and the relationship between plasticins structure and their presumed mechanisms of penetration into membranes (as illustrated in Figure 1).

![Figure 1: Penetration of the natural (0.1 µM ∆; 1.0 µM ▲) and modified plasticins (0.1 µM ○; 1.0 µM ●) into LPS-rich monolayers. Inset: adsorption of both plasticins at the free air/liquid interface.](image)